EXPERT OPINION

The therapeutic armamentarium in migraine is quite elderly

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Global Burden of Disease 2010 study considers migraine as one of the most important noncommunicable diseases in the world, classifying it third in terms of global prevalence (14.70%): it sums up the 54.19% of all the years of life lived with disabilities caused by the rest of all neurological disorders. This Editorial provides an historical excursus of old and new-entry molecules in migraine therapeutic area. Drugs for acute treatment such as triptans date back to the early 1990s with the appearance of sumatriptan and the following six triptans in the years immediately after (zolmitriptan, rizatriptan, naratriptan, eletriptan, almotriptan, frovatriptan). Prophylaxis drugs, dedicated to patients with medium/high frequency of crises, show as last entries topiramate and botulinum toxin type A. The use of this preventative group, with its intrinsic limits, is mandatory to reduce the risk of migraine chronification, a highly harmful clinical phenomenon that produces as its natural consequence the medication overuse headache. The development of new acute and preventative compounds, such as 5HT (serotonin) 1F receptor (5-HT1F) agonist lasmiditan, calcitonin gene related peptide (CGRP) peptide receptor antagonists, anti-CGRP monoclonal antibodies (LY2951742, ALD403, LBR101) and anti-CGRP-r monoclonal antibody (AMG334), is warranted and might be soon completed in order to offer new opportunities to migraine patients.

Keywords: 5-HT1F, burden of disease, CGRP, migraine, triptans

Expert Opin. Drug Metab. Toxicol. (2015) 11(2):175-177

1. The burden of migraine

Global Burden of Disease (GBD) 2010 study considers migraine as one of the most important noncommunicable diseases in the world, classifying it third in terms of global prevalence (14.70%) right after dental caries in adults (35.29%) and tension-type headache (20.77%). The same GBD 2010 study shows that migraine alone, stratifying the diseases by using the term disability (health loss) evaluated with years of life lived with disabilities (YLDs), sums up on its own the 54.19% of all the YLDs caused by the rest of all neurological disorders [1]. This incredible burden of headache disorders, ranked as leading cause of disability, has been calculated in the GBD 2010 study and is inserted into an overall increase of neurological diseases of 12.4% compared with the previous study (GBD 1990), while migraine alone showed an increase of 8.0% [1].

Furthermore, the calculus of the ictal disability, as short-term health loss relative to the acute peak of the disease, classifies migraine seventh [2]. Lastly, if we refer to the natural progression of migraine toward chronification we can calculate that 1 – 4% of the general population suffers from chronic migraine, complicated by medication overuse headache (MOH) [3]. This has been recently reported also in the joint analysis of lifting the burden and WHO in the atlas of headache disorders [4].

Considering this enormous epidemiological, social and economic impact of this disease [5], testified also from the direct and indirect sanitary costs caused by it [6],

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it is before our eyes how the need to act is urgent, developing pharmacological innovation in order to reduce this silent plague.

2. Actual therapeutic options in migraine

Furthermore, going through an historical *excursus* of new-entry molecules in migraine therapeutic area, it surprises how old these molecules are [7,8].

Considering the drugs for acute treatment, the turning point of the triptans introduction in the market dates back to the early 1990s, with the appearance of the sumatriptan, to which other six molecules followed in the years immediately after: zolmitriptan, rizatriptan, naratriptan, eletriptan, almotriptan, frovatriptan [9-13]. All of them, even though their pharmacokinetic properties were slightly different, had served with honor in the past quarter of a century but if we consider the overall positive cardiovascular risk–benefit safety profile [14], we cannot understand the reason why only the 25% of migraine patients received prescription based on this therapy [15].

On the other side of the therapeutic approach to migraine we find prophylaxis. Recently, much importance has been dedicated to the concept of prevention from migraine chronification, a well-known and highly harmful clinical phenomenon that produces as its natural consequence the MOH, entrenching a refractoriness often very difficult to eradicate [3,8].

On this line, migraine patients not responding to usual prevention therapies gained advantages from the use of topiramate, a drug borrowed from other clinical areas like epilepsy [16]. Unfortunately, such drug produces heavy side effects and it is hard to manage for the general practitioner who, seen the wideness of this phenomenon from an epidemiological point of view, must be put in the position to manage adequately not only the episodic but mostly medium/high-frequency forms of migraine [16].

This would enormously reduce the inflow toward high-specialization headache centers, reducing the alarming growth of the chronic migraine population complicated with MOH (1 – 4%) [3,4].

Lastly, another application of old drugs re-applied to migraine for serendipity deserves to be mentioned: botulinum toxin type A, approved in the treatment of chronic migraine [17], even though its exclusive hospital use and methods of administration do not allow general practitioners that capillary management of the disease WHO hopes for [4].

3. A call for new compounds in migraine

What is the message we can offer to the readers now? We hope that on the basis of the existing pipelines for migraine treatment, the development of these compounds might be soon completed in order to offer new opportunities to migraine patients.

Comforting results might come from 5-HT_{1F} agonist lasmiditan as alternative to triptans for migraine patients with cardiovascular complications [8]. Since there has been no new information on this drug in the past 2 years, we are looking forward for future development, including the availability of dose–response curves [18].

However, it is now clear that CGRP peptide receptor antagonists, like olcegepant or telcagepant, despite of their high efficacy have no future on the basis of their intravenous administration or liver toxicity limits, to be considered however as 'off-target effects' [8]. It is also clear that for the prophylaxis of episodic and chronic migraine, fully humanized mAbs that target CGRP or its receptor seems to be promising: starting 3 and 3b randomized controlled trials will clarify the early clinical findings suggesting good tolerability and efficacy.

Regarding this last point, the prevention as real central pillar of migraine treatment, we hope that the above-mentioned anti-CGRP monoclonal antibodies (LY2951742, ALD403, LBR101) and anti-CGRP-r monoclonal antibody (AMG334) might reach in due time the clinical use in order to reduce the natural path to chronification of migraine [8].

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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